

that are drawn to a method of epimerizing the hydroxy group of an aldol moiety in *any* compound; however, claim 45 is clearly limited to rapamycin, derivatives of rapamycin, and analogs of rapamycin that belong to the same inventive concept as claims 1-41 and 77. Finally, the Examiner does not address our request that claim 77 be grouped with claims 1-41 and 45. Accordingly, Applicant requests that the restriction requirement be reconsidered and/or revised.

Rejection of claims 1-41 under 35 U.S.C. §112, second paragraph:

Claims 1-41 remain rejected under 35 U.S.C. §112, second paragraph, as being indefinite. In particular, the Examiner states that the metes and bounds of the terms “aliphatic”, “acyl”, “heteroaliphatic”, “aryl”, and “heteroaryl”, and the phrase “pharmaceutically acceptable derivative” are not known. Applicant respectfully traverses these rejections.

Aliphatic

As discussed by Applicant in response to the previous Office Action, the term “aliphatic” is explicitly and clearly defined in the specification to encompass *any* aliphatic group:

The term “aliphatic” as used herein includes both saturated and unsaturated, straight chain (i.e., unbranched), branched, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. (page 30, line 34 – page 31, line 13).

This definition may be broad; however, breadth is not indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). A term is definite so long as a person of ordinary skill in the art would be able to tell whether his or her conduct lies within or outside the scope of claims that include the term. The Examiner has said that the metes and bounds of the term are not clear because the specification provides “mere examples” of aliphatic groups. Applicant disagrees. As noted above, the specification clearly states that the term “aliphatic” encompasses *all* aliphatic groups; that the specification also mentions specific examples of aliphatic groups that fall within this definition does not alter the definition. These examples serve solely to *illustrate* the definition and do not limit it.

Acyl

As noted by Applicant in response to the previous Office Action, “acyl” is an art-recognized term. An acyl group is any group having the formula RCO- (see, for example, American Heritage® Dictionary of the English Language, 4th Edition, 2000) . The various inorganic acids cited by the Examiner do not provide acyl groups. Again, the Examiner seems to draw confusion from instances in which the specification presents examples of groups encompassed by the term. Again, Applicant submits that presentation of illustrative examples does not limit the breadth of a term, and does not negate its clarity.

Heteroaliphatic

As discussed by Applicant in response to the previous Office Action, the term “heteroaliphatic” is explicitly and clearly defined in the specification to encompass *any* aliphatic group that includes one or more oxygen, sulfur, nitrogen, phosphorous, and silicon atoms (page 32, lines 1-4). Applicant recognizes that this term is broad, but submits that, as with the terms discussed above, its breadth does not reduce its clarity.

The Examiner asserts that the term “heteroaliphatic” is “not normal nomenclature”. Applicant respectfully questions this assertion and its significance. Applicant notes that the term is quite common in patent claims (a search of the U.S. Patent Office web site found 62 patents that issued in the past 6 years with the term “heteroaliphatic” in their claims). Furthermore, even if it were an unusual term, it is given a definition in the specification that is clear and precise. Those of ordinary skill in the art can recognize an aliphatic group including one or more oxygen, sulfur, nitrogen, phosphorous, and silicon atoms.

Aryl and heteroaryl

As discussed by Applicant in response to the previous Office Action, the terms “aryl” and “heteroaryl” are explicitly and clearly defined in the specification to encompass *any* cyclic or polycyclic group (or heterocyclic and polyheterocyclic) that includes 3-14 carbon atoms (page 32, lines 8-10). Applicant acknowledges the breadth of these terms but again submits that breadth is not indefiniteness. *In re Miller*, supra.

Pharmaceutically acceptable derivative

Examiner has maintained the assertion that Applicant's use of the phrase "pharmaceutically acceptable derivative" is unclear. As discussed by Applicant in response to the previous Office Action, the phrase "pharmaceutically acceptable derivative" is explicitly and clearly defined in the specification to encompass *any* pharmaceutically acceptable salt, ester, carbamate, or salt of such ester or carbamate, of such compound, or *any* other adduct or derivative which, upon administration to a patient, is capable of providing (directly or indirectly) a 28-epirapalog as described herein, or a metabolite or residue thereof (page 30, lines 23-27). The Examiner asks whether a pyrano derivative would or would not be a pharmaceutically acceptable derivative under the claim. Applicant respectfully submits that it would be if, upon administration to a patient, it is capable of providing a 28-epirapalog as described; otherwise, it would not be.

Rejection of claims 1-41 under 35 U.S.C. §103, in view of Grinfield et al.:

Claims 1-41 stand rejected under 35 U.S.C. §103 as being obvious in view of Grinfield et al. (PCT Publication No. WO 98/09972). More specifically, the Examiner states that (a) Grinfield et al. teaches isomers of the compounds in claims 1-41, (b) that an optically active isomer is unpatentable over a prior art racemate or optical isomer of opposite rotation in the absence of unexpected or unobvious beneficial properties (citing *In re Adamson et al.*, 275 F.2d 952, 125 USPQ 233 (CCPA 1960)), and further (c) that it has been well established that a compound which is isomeric with a compound of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound (citing *In re Norris*, 179 F.2d 970, 84 USPQ 458 (CCPA 1950)). Applicant respectfully traverses this rejection.

The present claims recite compounds that are epimeric with rapamycin at position 28 (position 31 in Grinfield et al.'s nomenclature – "C28/31"). Grinfield et al. teach only one compound having the claimed stereochemistry at this position, and that compound is also epimeric with rapamycin at position 43 (position 42 in Grinfield et al.'s nomenclature – "C43/42"). Grinfield et al. *do not* disclose compounds that are epimeric *only* at C28/31. Grinfield et al. summarize their invention by stating: "The rapamycin compounds of this invention are either epimeric (S-configuration) with rapamycin at position 42 *alone* or positions

31 and 42, [...]” (page 2, lines 34-35). Thus, Grinfield et al. exclude compounds that are epimeric *only* at C28/31.

There is a simple explanation for this exclusion: Grinfield et al.’s chemistry did not and cannot epimerize *only* C28/31. In fact, the relevant chemistry described in Grinfield et al. (Example 14 on page 12) may not have produced the C28/31 epimer at all. Applicant points out that the same researchers reported in a different application (PCT Publication No. WO 98/09970) that very similar reaction conditions (triflation of the C28/31 alcohol followed by introduction of an external nucleophile, in this case water) produce allylic rearrangements rather than epimerization. Furthermore, the cited Grinfield et al. application provides only general spectroscopic measurements (partial proton NMR, MS, and partial IR) as the basis for concluding that the C28/31, C42/43 bis-epimer was produced. These, data however, are consistent with *numerous different* diastereomers of rapamycin. It is unclear from these data that the researchers ever accomplished epimeric conversion at C28/31. Even if such conversion was achieved, however, the Grinfield et al. compound was also epimeric at C42/43.

The Grinfield et al. disclosure provides no motivation for one of ordinary skill in the art to pursue preparation of a compound epimeric *only* at C28/31 (i.e., and not also epimeric at C42/43). In fact, Grinfield et al., teach that desirable rapamycin derivatives have immunosuppressive activity. The data that they report for their supposed C28/31, C42/43 *bis*-epimer compound show relatively low activity as compared to rapamycin (Table 1 on page 18) and therefore suggests that similar compounds are actually *undesirable*.

Moreover, even if a person of ordinary skill in the art, reading Grinfield et al. *wanted* to make a compound that is epimeric at C28/31 but not C42/43, s/he would not have the tools to do so. As noted above, Grinfield et al. may not have even made the compound they reported; their chemistry could not make the compounds we claim. The present inventors developed entirely new chemistry, that allowed an unprecedented and unexpected epimeric conversion at position C28/31. Grinfield et al. could not render obvious this chemistry, or the compounds it enables.

The present situation is entirely different from that in the cases, *In re Adamson et al.*, 275 F2d 952, 125 USPQ 233 (CCPA 1960) and *In re Norris*, 179 F2d 970, 84 USPQ 458 (CCPA 1950) cited by the Examiner. It is true that the cited cases describe situations in which a later-claimed compound was found to be obvious over a previously disclosed isomer. However, the

question was (and is) not merely whether the compounds are isomeric, but whether the earlier disclosure was sufficient to put the later-claimed isomer in the public domain. *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). Until such a determination has been made, a rejection for lacking unobvious or unexpected beneficial properties cannot and should not be made. In particular as a matter of Patent Office practice:

“If the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on the close relationship between their structures and those of prior art compounds.” MPEP §2144.09.

As noted above, the methods taught by Grinfield et al. cannot be used to prepare the claimed compounds.

In *Adamson et al.* the claimed stereoisomer was found to be obvious over a prior disclosure of a racemic mixture of the same compound. Various methods for resolving stereoisomers were known in the art at the time, and Adamson used a known method to isolate his isomer. Thus, in *Adamson et al.*, the prior disclosure *included* the claimed compound, *and enabled* its preparation. Such is not the present case.

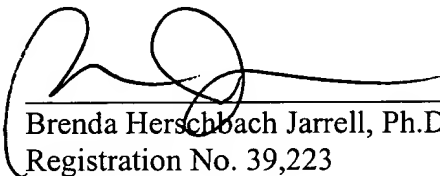
In *Norris*, the compound at issue was very simple, having the formula: $\text{CH}_3\text{-CH}(\text{CH}_3)\text{-C}(\text{NH})\text{-C}(\text{CH}_3)_2\text{-CN}$. It was rejected over a prior disclosure of a different compound with the same number of carbon (8), hydrogen (14), and nitrogen (2) atoms, in a different arrangement. The court made clear that the rejection was based on an established principle that compounds of the same chemical formula tend to have similar or identical chemical and physical properties (“a homologous series of chemical compounds possess the same principal characteristics which vary gradually from member to member, and that knowing the chemical and physical properties of one of the members suggests the properties of the other members”, 84 USPQ 460). This may be true of simple compounds of the type at issue in *Norris*. It is not generally true of complex compounds, and is certainly not true of rapamycin. Rapamycin has 51 carbons, 74 hydrogens, 1 nitrogen, and 13 oxygens. There is no reason to believe or expect that every rapamycin isomer will behave similarly to every other rapamycin isomer. In fact, as discussed in response to the

previous Office Action, the rapamycin compound has proven to be unusually sensitive to change, so that seemingly small structural modifications often have dramatic changes in chemical properties.

Conclusion

For the reasons presented above, it is submitted that the pending claims are allowable over the art of record. Please charge any fees that may be required, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,



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